PARAPHENYLENEDIAMINE SENSITIVITY

Possible Cross-Sensitization to Amines Present in Rubber

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An indication that paraphenylenediamine (PPD) sensitivity might point to a rubber dermatitis was found in a report by Sidi and Dobkevitch-Morrill (1). These authors described six cases of rubber dermatitis, five of whom showed 1 to 3 plus patch test reactions to PPD. In addition and fairly often, positive patch tests have been obtained to rubber with negative tests to monobenzyl ether of hydroquinone, mercaptobenzothiazole and tetramethylthiuram monosulfide (2) suggesting the need to look further for the presence of sensitizers in rubber products.

This subject was studied by testing six cases, known to be sensitive to PPD with a series of amines used as ingredients of antioxidants in rubber. The positive patch tests to PPD were characterized by pruritus, bright erythema and a button-like induration. Vesicle formation was not evident. Persistence of the positivity for several weeks or longer was a constant feature. All the cases had been patch tested previously with the following test substances: potassium chromate 1% aqueous, nickel sulfate 1% aqueous, mercuric chloride 0.1% aqueous, formaldehyde 1% aqueous, monobenzyl ether of hydroquinone 1% petrolatum, mercaptobenzothiazole 1% petrolatum, tetramethylthiuram monosulfide 1% petrolatum, PPD 2% petrolatum, benzocaine 1% petrolatum, rhus resin 0.1% petrolatum, and thiosalicylic acid 0.1% petrolatum. As indications arose, other test substances were included. The PPD sample was renewed about every three months. The over-all preponderance of negative tests makes it unlikely that primary irritation occurred from either fresh or older test samples.

The amines tested and their formulas appear in Table 1. They were tested in concentrations of 1 per cent in petrolatum. Twenty-five subjects were patch tested for evidence of primary irritation. No reactions occurred. A number of the amines had been screened by Blank and Miller (3). This assured the testing of substances without using completely unknown chemicals. They recorded one response to phenyl alpha naphthylamine, one to a reaction product of diphenylamine and acetone and one to a butyraldehyde-aniline condensation product. The patients were told in advance the nature of the tests and warned to remove the patch at once if any symptoms developed. The tests were read in 24 hours and inspected at intervals for several weeks.

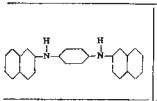
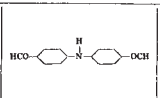
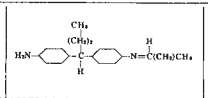
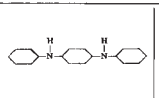
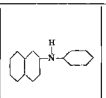
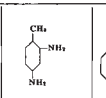
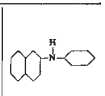
The attacks of dermatitis in the cases are also summarized in the table. Notable differences are apparent. Patients 1 and 2 had had trivial episodes; 3 had had several fairly extensive occurrences, but involution was prompt and uneventful. These subjects had developed no known systemic drug intolerances. Dermatitis from dyed clothing was incriminated by 1, 3, 5 and 6. Efforts to substantiate this by patch test were not successful. Patients 4 and 5 stand out because of their high attack rate of dermatitis, chronicity of recurrences and the final development of localized neurodermatitis. Their reactions to drugs had been frequent, severe and extensive. Patient 5 dated the onset of dermatitis to the use of brown hair dye. Patient 6 was vague about any drug reactions. The PPD test was delayed 72 hours. Penicillin injections in 1956 for a pedal dermatitis were stopped because of swelling of the feet. The use of procaine the same year caused swelling and soreness of the gums. Trauma from dental extraction could not be ruled out. 7 was included to emphasize that PPD and benzocaine patch tests often react together, but benzocaine can also react quite independently.

The PPD tests in patients 1, 2, and 3 were indistinguishable by inspection from the PPD tests in 4 and 5, yet the amines in 1, 2 and 3 were easily tolerated. An explanation for these findings may be the fact that 4 and 5 had had reactions from oral and parenteral drugs. These reactions appeared to furnish some essential link and to determine the broadness of the sensitization. The PPD test in 3 was reactive enough to weep for several days. The amines were tested before this reaction subsided. Still, they were tolerated without incident. "Caine" sensitivity was present in 4 and 5. This was not a determinate because patient 7 had had an extensive weeping dermatitis from this sensitivity. Notwithstanding, the amines were tolerated without evidence of any irritation.

It is of interest that Fisher and Sturm (4) dem-

TABLE 1

Correlation of PPD sensitivity and amine patch test results

Attacks of Dermatitis vs. Drug Reactions					Amines Used as Ingredients of Rubber Antioxidants						
Case no., sex, and age	Attacks of dermatitis	Drug reactions: Positive patch tests	Oral	Injection	 Di-beta naphthol-P-phenylene diamine	 4-4 Dimethoxy Diphenylamine	 Butyraldehyde aniline condensation	 Diphenyl p-phenylene diamine	 Phenyl-a-naphthyl-amine	 2-4 Toluene diamine	 Phenyl-b-naphthyl amine
1, F, 20	2	RHUS		Procaine 0 Penicillin 0							
2,* M, 60	1	RHUS Monobenzyl ether of hydroquinone	Sulfa 0 Mycin 0	Procaine 0 Penicillin 0							
3, M, 50	3		Sulfa 0	Procaine 0 Penicillin 0							
4, M, 46	7 Neurodermatitis	Benzocaine Procaine P-Amino-Benzoic Acid Chromate Mercury	Sulfa '47 Sulfa '54	Penicillin Hives, swelling '47 Hives, swelling '55 Procaine Swelling, pain '56 Swelling, pain '58			4-plus			4-plus	
5, F, 28	8 Neurodermatitis	Procaine	Sulfadiazine '50	Procaine penicillin Hives, rash '50 Procaine Swelling, pain '58 Swelling, pain '58 "Passed out"			4-plus			4-plus	

6, F, 41	7		Sulfa 0	Penicillin? '56 Procaine? '56		4-plus					
Benzocaine Sensitivity Alone:											
7, F, 61	3	Benzocaine '57 Benzocaine '59	Sulfo 0	Penicillin 0 Procaine 0							

* Chronic cheilitis with final carcinoma.

onstrated that allergic eczematous sensitivity to procaine is not accompanied as a rule by the vascular or anaphylactoid allergy. Cases 1, 2, and 3 would seem to fall in this category. Their allergic state was confined to the skin, perhaps only epidermal in extent and depth. Patients 4 and 5, and possibly 6, seemingly had a combined type of sensitivity both deep and superficial. A subcutaneous tissue reaction to dental procaine, manifested by local swelling and tenderness, apparently elaborated an antigen that markedly influenced the sensitization spectrum to include in this instance the amines present in rubber. There, of course is always the possibility that previous sensitization might have occurred from past contact with rubber, and the reaction to the amines are examples of multiple rather than cross sensitivity.

DISCUSSION

Mayer (5) states that PPD and azo-dyes are only indirect antigens and require metabolic transformation before they become direct or active antigens. Baer and Witten (6) point out that cross-sensitization occurs between immunochemically closely related substances or where two or more previously unrelated compounds through conversion in human tissue are broken down into products which are immunochemically related. It is tempting to speculate that in epidermal sensitivity, specificity holds true and multiple sensitivities may or may not be present; whereas in deep tissue reactions from drugs, their metabolites, end products of conversion, and/or detoxification furnish haptens that broaden the sensitization pattern for the respective antigens.

Fisher and Sturm (4) also found that there was no widening of the cross-sensitization pattern despite repeated exposures to the primary allergen which were sufficiently intense to produce severe dermatitis as well as exposure to potential secondary allergens. Baer and Witten (7) in commenting on this article state that the spectrum of cross-sensitivity to PPD appears to be related to an individual "host" factor and to be established early. It is possible that this "host" factor may be related to the development of deep tissue reactions to drugs. Adriani (8) writes that "it has been well established that procaine is hydrolyzed in the tissues into para-aminobenzoic acid and diethyl amino ethanol. The para-aminobenzoic acids conjugated with glycine in some cases and excreted in the urine. In other cases it is methylated; in other cases it is eliminated unchanged." If the make up of the procaine molecule could be suitably tagged and injected into a procaine sensitive subject, it might be possible to trace the portion of the molecule and its distribution that forms the sensitizing antigen.

SUMMARY

A number of amines used as rubber antioxidants were patch tested for evidence of cross sensitization with PPD. A history of systemic drug reactions appeared to be a determinate factor. In the absence of these, the amines were tolerated without incident; but where there had been systemic reactions from procaine, sulfonamides and penicillin (procaine), positive patch tests developed to butyraldehyde aniline condensation product and 2,4-toluene diamine. These reactions reproduced the intensity of the previous reaction to PPD.

The findings suggested that a positive patch test to PPD might indicate a sensitivity of one or more types: 1) epidermal and/or eczematous sensitivity alone, 2) combined epidermal and systemic sensitivity occurring from previous drug reactions. The latter one was the type in which possible cross reactions to the amines occurred. A positive patch test to PPD is a clinical indication of possible rubber sensitivity.

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